

# ACTIVE CHRONIC HEPATITIS : Part I

by

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## INTRODUCTION

IN 1950 Waldenström first drew attention to the occurrence of a form of chronic liver disease in young people, predominantly adolescent girls, in whom there was moderate jaundice, enlargement of the liver and spleen, acne, amenorrhoea and hyperglobulinaemia. The occurrence of fever, arthralgia and Cushingoid features was noted (Kunkel et al 1951, Bearn et al 1956), the LE cell phenomenon was reported (Joske and King 1955) and the condition was called lupoid hepatitis (Mackay et al 1956). Over the years it has been given many other names including liver disease in young women (Bearn et al 1956) with hypergammaglobulinaemia (Jones and Castleman 1962), active juvenile cirrhosis (Read et al 1963), plasma cell hepatitis (Page et al 1964), autoclastic lupoid hepatitis (Naish 1960) and auto-immune hepatitis (Mackay et al 1965), each emphasising particular pathological or clinical features. In recent years the term active chronic hepatitis has gained general acceptance because it embodies two of the essential pathological and clinical features of the disorder, namely its chronic and therefore usually progressive nature and the activity of the process typically manifested by the recurring episodes of hepatitis which punctuate its course. Lately Sherlock (1975), with a view to further refining the nomenclature of chronic hepatitis, has proposed that the classical type be called active chronic "lupoid" (HBAG negative) hepatitis.

Although the main pathological process occurs in the liver the striking immunological disturbance and the wide spectrum of symptoms indicate that it is a systemic disease. Discussion continues on the role of altered immune responses in the pathogenesis of active chronic hepatitis, and the absence of a marker for the virus of hepatitis A has been a great obstacle to progress. It seems probable that liver cell damage caused by a variety of agents including drugs (Reynolds et al 1971, Hoyumpa and Connell 1973, Russell et al 1973) may, in susceptible individuals, initiate self-perpetuating hepatitis. The growing belief that genetic factors may predetermine the susceptibility of the host has been strengthened by the discovery of a high prevalence of antibodies and of abnormal levels of immunoglobulins in relatives of patients with active chronic hepatitis, and also by a significant associated incidence of diseases which are normally regarded as having an immunological basis (Galbraith et al 1974). The high frequency of histocompatibility antigens HL-A 1 and HL-A 8 in patients with HBAG negative active chronic hepatitis is in sharp contrast with the normal frequency of HL-A 1 and the

total absence of HL-A 8 in patients with HBAG positive active chronic hepatitis (Galbraith et al 1974). The experimental production of a chronic aggressive hepatitis-like lesion in rabbits by prolonged immunisation with human liver-specific lipoprotein, and the confirmation of the presence of hypersensitivity to human liver-specific lipoprotein in patients with active chronic hepatitis, have underlined the probable role of disturbances of cellular immunity in the pathogenesis of active chronic hepatitis. It seems likely that the non-organ-specific auto-antibodies (anti-nuclear antibody, smooth muscle antibody and mitochondrial antibody) merely reflect an abnormal immune system, perhaps genetically determined, and stimulated to auto-antibody production by viral or drug-induced hepatic damage (Smith et al 1975).

#### DEFINITION

Active chronic hepatitis is an inflammatory disease of the liver which has a variable and usually unremitting course characterised by the clinical, laboratory and histological changes of both active and chronic hepatitis. While a presumptive diagnosis can often be made from the clinical and laboratory data, a definitive diagnosis requires histological examination of the liver, for only in this way may it be possible to differentiate active chronic hepatitis from prolonged virus hepatitis, chronic persistent hepatitis, primary biliary cirrhosis and certain other disorders.

#### PATIENTS

The 40 patients who form the basis of this investigation were seen personally at the Royal Victoria Hospital during the 15-year period 1961–1975 and include all those in whom a firm diagnosis of HBAG negative active chronic hepatitis was made. Many of them continue to attend the Liver Clinic regularly and have been followed up for between four months and 13 years, the mean follow-up being five and a half years.

In general the diagnosis was based on the history and clinical findings, the biochemical, haematological and serological data and the information provided by histological examination of the liver. Those patients in whom liver biopsy was initially omitted, contraindicated or refused (4) or was technically unsuccessful (2) were accepted on the strength of the other evidence available.

A diagnosis of active chronic hepatitis is entertained when there is clinical or biochemical evidence of inflammatory liver disease for a period of at least six months. It must be distinguished from prolonged virus hepatitis and chronic persistent hepatitis both of which are likely to heal completely without treatment. Active chronic hepatitis associated with HBAG and that due to the administration of drugs such as oxyphenisatin, methyldopa, isonicotinic acid and, rarely, chlorpromazine. Wilson's Disease and alpha<sub>1</sub> antitrypsin deficiency also have to be kept in mind.

## PATHOLOGY

Liver histology was available in 35 patients, in 27 following percutaneous needle liver biopsy and in a further 7 following wedge biopsy obtained at laparotomy. The only histological material available in one case was obtained at autopsy more than four years after the onset of the illness.

In 29 cases the appearances were those of active chronic hepatitis in various stages of activity and progression (De Groote et al 1968, Scheuer 1968). In 13 there was perilobular liver cell degeneration and necrosis with collapse of the reticulin framework particularly in the neighbourhood of the portal triads and resulting in disruption of the limiting plates. Piecemeal necrosis was noted and the severity of the parenchymal lesion varied considerably from lobule to lobule. A striking inflammatory cell infiltrate, consisting mainly of lymphocytes with plasma cells and some polymorphs and eosinophils, was usually concentrated in and around the enlarged portal tracts. In some cases lymphoid follicles were present and the inflammatory cells extended into the lobules to a varying degree. Fine fibrous septa were seen to radiate from the portal tracts and to divide up the liver lobules into clumps of cells from which early regenerative nodules might be expected to arise and in 11 cases irregular parenchymal regeneration, intralobular septa formation and portal tract fibrosis indicated the development of early cirrhosis.

In five cases the initial appearances of acute, mainly perilobular, hepatitis were seen to give way in subsequent biopsies to those of early active cirrhosis or late relatively inactive cirrhosis with little continuing liver cell necrosis or inflammatory cell infiltration.

There were two patients in whom the initial biopsy was performed either too early, and merely showed the changes of acute hepatitis, or too late when post-necrotic cirrhosis had already developed. In three patients diagnoses of chronic persistent hepatitis, primary biliary cirrhosis, and ? hepatitis ? cholangitis were suggested but these patients were also accepted on the basis of the other information available. Two patients in whom liver biopsy showed chronic aggressive hepatitis and early cirrhosis with persistent activity respectively, but with clinical features of advanced cirrhosis with portal hypertension, were excluded from the series. Others with clinical and biochemical features in keeping with active chronic hepatitis but with the histological changes of well developed cirrhosis were also omitted.

The possible effects of sampling error, progression from one type of liver disorder to another and changes brought about by moderate dosage immunosuppressive therapy were observed in two patients. In the first, the initial biopsy showed the changes of chronic persistent hepatitis whereas 33 months later, in the absence of treatment, a further biopsy showed active chronic hepatitis with early cirrhosis. In the second patient, the appearances in the initial biopsy were those of active chronic hepatitis but after 14 months corticotrophin therapy the second biopsy showed chronic persistent hepatitis.

The patchy distribution of the pathological changes in the liver, the small amount of tissue available for examination and the performance of the biopsy too early or too late in the course of the illness may greatly detract from the value of the information which such an examination would be expected to provide. Sherlock (1975) stresses that serial liver biopsies may be necessary to make a diagnosis of active chronic hepatitis. Cirrhosis is said to develop early in the course of the disease and to be already present in one-third of cases when the diagnosis is first made. Within two years of the onset some degree of cirrhosis is almost inevitable. Recurring episodes of necrosis with further stromal collapse and fibrosis lead to increasingly severe macronodular cirrhosis often with shrinkage of the liver.

## CLINICAL FEATURES

### *Age and Sex*

The age at onset ranged from 9 to 74 years and in 28 patients (70 per cent) symptoms commenced between the ages of 30 and 59. This contrasts sharply with the experience of others (Mistilis and Blackburn 1970, Sherlock 1975) who reported that half of their patients were in the age groups 10–30 and 10–20 respectively. On the other hand Soloway et al (1972) found the onset to occur after the age of 40 in approximately 60 per cent of cases.

It is possible that the differences between these series in the age of onset of active chronic hepatitis are due in part to differences in the populations from which the cases are drawn. In view of the fact that in Belfast there are two busy teaching hospitals devoted to the care of sick children and a large infectious diseases hospital to which cases of virus hepatitis in children and adults are admitted, it would not be surprising if a series of patients seen only at the Royal Victoria Hospital contained a relatively small proportion of those in the first two decades of life. As anticipated there was a considerable female preponderance—28 out of 40 (70 per cent).

### *Previous History*

In six patients there was a previous history of jaundice highly suggestive of hepatitis A. The illness occurred between the ages of 5 and 9 in three patients and at 20, 29 and 42 in the other three. The intervals between these episodes of jaundice and the onset of active chronic hepatitis were 53, 26, 37, 26, 26 and 17 years respectively.

### *Family History*

A history of jaundice, probably due mainly to hepatitis A, was obtained in near-relatives of seven patients. Thyroid disease occurred in the immediate families of 10 patients and there were at least six cases of thyrotoxicosis. Diabetes was reported in five families and where this was insulin-dependant, the patient also had insulin-dependant diabetes which long preceded the onset of the liver disorder. Major allergy, anaemia and rheumatic fever were each noted in three families but there were no instances of ulcerative colitis, rheumatoid arthritis or systemic lupus erythematosus.

### *Onset of the Disease*

In 26 patients (65 per cent) the illness began abruptly and was indistinguishable from acute virus hepatitis. In at least two cases, a boy aged 9 and a girl of 15, the illness occurred when other children in the same class at school had hepatitis A. Symptoms such as anorexia, nausea, vomiting, fatigue, malaise, fever, polyarthralgia, right upper abdominal discomfort and the passage of dark urine usually developed over a period of one to two weeks by which time jaundice was apparent.

In the majority of cases of acute onset symptoms died down after a few weeks. Jaundice faded, hepatic tenderness and enlargement diminished and the various laboratory tests showed improvement. In a small minority of such patients (4) all symptoms and clinical signs of the disorder disappeared completely without any treatment but there was persistent elevation of serum transaminase and gammaglobulin levels. After an interval of a few weeks or months (and in one instance 5 years) these patients suffered a hepatic relapse with recurrence of symptoms closely resembling those at the onset of the illness. In a good many more patients (10) recovery began but was incomplete. Appetite and energy were not fully restored, jaundice faded but did not disappear and some liver enlargement remained. After a few weeks or months there was further deterioration of appetite and energy, nausea returned, jaundice deepened and hepatic tenderness reappeared. Some patients experienced several such remissions and relapses in the space of 6-9 months. In yet others (11) the expected recovery failed to occur and the symptoms of onset persisted in varying degree. Disinclination for food coupled with sickness and occasionally troublesome diarrhoea led to considerable weight loss and debility. In some the disorder followed a fluctuating course with variation in the severity of the symptoms and clinical findings from month to month. After recovery from the hepatic illness one patient developed painful swelling of many of the limb joints. In another an erythematous rash considered to be typical of lupus erythematosus appeared across the bridge of the nose and there was painful swelling of a number of the finger joints. LE cells were present in both patients. Although jaundice was absent, the liver was enlarged and firm and serum transaminase and gammaglobulin levels were considerably elevated.

In 14 patients (35 per cent) the onset of the illness was insidious and symptoms developed over a period of 3 to 14 months. They included polyarthralgia and sometimes swelling of the affected joints, unaccustomed tiredness, an indifferent appetite, occasional mild nausea, considerable loss of weight, a degree of malaise, unexplained fever, an unhealthy colour and the eventual appearance of overt jaundice. One patient however, a girl of 13, has not been noted to be jaundiced at any time since the onset of the illness. In the four patients in whom polyarthralgia was the first symptom, the joints usually affected were the fingers, wrists, knees, ankles and feet and they were often tender and sometimes slightly swollen. A diagnosis of early rheumatoid arthritis was made in two of them and appropriate treatment was commenced. Three to 14 months after the onset of polyarthralgia, symptoms of hepatitis developed acutely in two patients and insidiously in the other two patients.

### *Established Disease*

As the months passed and the disease progressed, the syndromes of onset made way for the gradually emerging clinical picture of active chronic hepatitis. Many of the early symptoms remained but others were added and examination disclosed a number of striking new physical signs.

Tables I and II show the principal clinical features in the 40 patients at the time of diagnosis. Those symptoms occurring most frequently during the course of the illness were fatigue, rapidly dissipated energy, an indifferent appetite, intermittent

TABLE I  
*Symptoms in 40 patients with untreated active chronic hepatitis*

|                                       | <i>Number</i> | <i>Percentage</i> |
|---------------------------------------|---------------|-------------------|
| Fatigue .....                         | 31            | 78                |
| Anorexia .....                        | 30            | 75                |
| Nausea with or without vomiting ..... | 26            | 65                |
| Weight loss .....                     | 22            | 55                |
| Fever .....                           | 18            | 45                |
| Itching .....                         | 14            | 35                |
| Abdominal discomfort .....            | 11            | 28                |
| Polyarthralgia .....                  | 10            | 25                |
| Amenorrhoea .....                     | 7             | 64*               |
| Epistaxis .....                       | 5             | 13                |
| Diarrhoea .....                       | 5             | 13                |

\* There were 11 premenopausal female patients

nausea and in over half the patients weight loss ranging from 4 to 40 lb (1.8–18 k) with an average of 15 lb (6.8 k). Almost half the patients were feverish and in 10 out of 18 this exceeded 100°F (37.8 C).

In 9 of the 11 patients with abdominal discomfort the illness had commenced as acute hepatitis and the incidence of hepatic enlargement and tenderness was above average. Enlargement of the liver was usually present from the onset and when the disease became established, firm smooth hepatomegaly was the rule with tenderness in about one-third of cases. In 12 (30 per cent) there was considerable hepatic enlargement, the lower edge of the right lobe being felt 3–4 finger-breadths (fb) (6–8 cm) below the right costal margin in full inspiration.

Enlargement of the spleen was felt in 16 patients (40 per cent) at the time of diagnosis and in 6 the lower pole could be felt 2–4 fb (4–8 cm) below the left costal margin in full inspiration. In only four of the patients with splenomegaly was there any suspicion of cirrhosis and none of them had very large spleens. In 11 LE cells were detected and in six they were found regularly and at times in considerable numbers.

TABLE II

*Clinical findings in 40 patients with untreated active chronic hepatitis*

|   | <i>Number</i> | <i>Percentage</i> |
|---|---------------|-------------------|
| Jaundice  | 37            | 93                |
| Hepatomegaly  | 33            | 83                |
| Hepatic tenderness                                  | 14            | 35                |
| Splenomegaly  | 16            | 40                |
| Oedema, ascites and encephalopathy                  | 1             | 2.5               |
| Vascular spiders                                    | 19            | 48                |
| Dilated facial venules                              | 12            | 30                |
| Palmar erythema                                     | 9             | 23                |
| Acne  | 3             | 7.5               |
| Polyarthrits  | 5             | 13                |
| SLE rash  | 3             | 7.5               |
| Pleurisy and pericarditis with effusion             | 1             | 2.5               |
| Bilateral pneumonitis and pleurisy<br>with effusion | 1             | 2.5               |
| Thyroid enlargement                                 | 4             | 10                |

Jaundice was present in all but three patients at the time of diagnosis. It was mild in 19 and deep in 11. Itching occurred in one-third of the patients and correlated surprisingly poorly with the intensity of jaundice, being present in only 6 of the 11 most deeply icteric patients. There was no better correlation between itching and high serum alkaline phosphatase levels, only 6 of the 13 patients with serum alkaline phosphatase levels above 30 King Armstrong units complaining of itching.

Vascular spiders were present in almost half the patients but only five patients (13 per cent) had more than five spiders. However the presence of vascular spiders and dilated facial venules proved useful in raising the index of suspicion of active chronic hepatitis in patients with nondescript symptoms and few other physical signs.

Only one patient developed oedema, ascites and mild hepatic encephalopathy early in the course of the illness before treatment was commenced. He made a slow but eventually excellent recovery and remains well 11 years later, never having had any recurrence of liver cell failure or hepatic encephalopathy. Transient encephalopathy occurred in one other very deeply jaundiced patient as treatment with prednisolone was being introduced. There was no accompanying oedema or ascites and she also made a rapid recovery. Years later she developed macronodular cirrhosis with portal hypertension and variceal bleeding but when last seen 11 years after the onset of the illness had no fluid retention and was mentally clear.

### *Systemic Manifestations and Associated Conditions*

“Active chronic hepatitis of lupoid type is not a condition confined to the liver” (Sherlock 1975). It is a systemic disease in which almost half the sufferers have associated conditions which are apparently unrelated to the liver. Among these are polyarthralgia, polyarthritis, a variety of skin lesions including those of lupus erythematosus, pericarditis, myocarditis, pleurisy, transient pulmonary infiltrations, fibrosing alveolitis, glomerulonephritis, renal tubular acidosis, the sicca syndrome, ulcerative colitis and a number of endocrine disorders such as amenorrhoea, Cushing’s syndrome, diabetes and various thyroid abnormalities including Hashimoto’s thyroiditis. These extra-hepatic syndromes may precede, coincide with or more frequently follow the onset of clinical liver disease but in general the clinical picture is dominated by the features of the hepatic lesion.

Amenorrhoea was often present from the beginning of the illness and became established in 7 of the 11 premenopausal patients but other endocrine disorders such as obesity, facial mooning, striae livida and hirsutism, traditionally associated with active chronic hepatitis, did not occur and acne was observed in only three patients prior to the commencement of corticosteroid or corticotrophin therapy. This may be partly due to the small number in this series of girls and young women in whom such symptoms are said to occur most commonly.

Three patients, each with a direct family history, had insulin-dependant diabetes which long preceded the onset of active chronic hepatitis. Of the five patients with a thyroid disorder two had non-toxic goitre, one had thyrotoxicosis, another had thyrotoxicosis treated with radioactive iodine years prior to the onset of active chronic hepatitis and the fifth patient was found at autopsy to have lymphocytic thyroiditis.

Polyarthralgia with or without swelling and tenderness of the affected joints was an important symptom in ten patients (25 per cent) and tended to occur at the onset or early in the course of the established disease. The joints most frequently affected were the metacarpo-pharyngeal and proximal interphalangeal joints of the fingers, the wrists, elbows, ankles and knees. There was no evidence of erosive arthritis nor were there any of the extraarticular manifestations of rheumatoid disease. The Rose Waaler D.A.T. was positive in two patients and then only intermittently and in low titre. In nine of the ten patients however the LE cell phenomenon was positive and repeatedly so in six patients.

Skin rashes accepted as lupus erythematosus by dermatologists occurred in three patients. In two patients typical butterfly rashes were seen on the face and there were two instances of widely distributed lesions on the limbs.

Pericarditis and bilateral pleurisy with effusion occurred two or three months after the onset of acute hepatitis in one patient in whom LE cells were repeatedly demonstrated. A complete clinical recovery occurred over a period of six months without treatment but the electrocardiogram did not return to normal for almost one year and the serum transaminase and gammaglobulin levels remained elevated. In another patient pneumonitis and bilateral pleurisy with effusion occurred four

months after the onset of the illness which was characterised by polyarthritis. LE cells were also demonstrated repeatedly in this patient whose condition did not begin to improve until prednisolone was given in high dosage. During life this patient did not exhibit any signs of renal or thyroid disease but was found at autopsy to have electron microscopic appearances diagnostic of the renal lesion of lupus erythematosus and the histological changes of lymphocytic thyroiditis suggestive of Hashimoto's disease.

Diarrhoea was a prominent symptom from the onset of the illness in five patients, only disappearing in three patients when corticosteroid or corticotrophin therapy was commenced and continuing in the other two. The changes of ulcerative colitis have not been demonstrated in any of these patients though this condition has been reported to occur in up to 11 per cent of cases of active chronic hepatitis (Mistilis 1969). Instances of the sicca syndrome, renal tubular acidosis and interstitial pulmonary fibrosis were not observed in this series.

#### *Course of the Disease*

From time to time the tempo of the illness quickened with the occurrence of episodes of active hepatitis or polyarthritis. While these were most frequent early in the course of the disease, patients remained liable to such reactivation many years after the onset. Of the 40 patients in this series, 30 suffered a total of more than 56 relapses while not receiving treatment, and 47 of these episodes seemed to be purely hepatic in type. Six relapses, all occurring in the same patient, were characterised by painful and swollen joints, a butterfly rash on the face and splenomegaly, but with no clinical or biochemical evidence of reactivation of the liver lesion save in one episode. In another patient the relapse consisted solely of polyarthritis and there was no evidence of accompanying liver involvement. In the remaining two relapses, patients had painful swollen joints and also symptoms and signs of active hepatitis.

In some of the relapses, symptoms came on quickly while in others they developed insidiously over a period of several weeks. They often closely resembled those which originally ushered in the illness. They varied in severity from little more than tiredness, malaise and an indifferent appetite with moderate elevation of serum transaminase and gammaglobulin levels to grave illness with deep jaundice, peripheral oedema, ascites and hepatic encephalopathy. Three of the relapses were symptomless and were discovered only as a result of routine biochemical screening. Some occurred spontaneously while others were precipitated by intercurrent infection especially influenza and other virus infections. Similar relapses have been seen in patients receiving corticosteroid or corticotrophin therapy and have often followed injudicious reduction of dosage or premature withdrawal of treatment.

Minor relapses sometimes resolved spontaneously but the initiation of effective treatment usually brought about a quick remission so that even those with evidence of serious liver-cell failure made a remarkable recovery over a period of a few weeks or months.

Often between such episodes appetite and energy returned, jaundice vanished and hepatic tenderness and enlargement disappeared. In some, evidence of a persisting hepatic disorder was to be found only by repeating the relevant biochemical tests though it is well recognised that the histological abnormalities remain. The disease is said ultimately to become inactive in about 40 per cent of cases by which time established cirrhosis is present. At the other extreme however the course of the disease is progressively downhill and as cirrhosis advances the liver shrinks, portal hypertension develops and the spleen enlarges. Episodes of variceal bleeding occur and there is increasingly severe liver cell failure and hepatic encephalopathy.

Active chronic hepatitis is a disease in which there is considerable morbidity. During the early stages, this is due to the fluctuating course with episodes of active hepatitis and to persisting debility, but during the later stages it results mainly from the complications of cirrhosis. The mortality rate is also high particularly in the early stages when activity of the process is greatest and the prognosis is said to be somewhat better in patients who survive the first two or three years. Death is usually due to liver cell failure, sometimes precipitated by gastro-intestinal haemorrhage but septicaemia, associated ulcerative colitis or the complications of prolonged corticosteroid or corticotrophin therapy may also contribute.

#### HAEMATOLOGICAL, BIOCHEMICAL AND SEROLOGICAL FEATURES

The serum haematological and biochemical findings are shown in Table III. For each investigation the immediate pre-treatment result or the mean of several results for each patient was used to calculate the median and range for the whole group.

TABLE III  
*Haematological and biochemical findings in patients with untreated active chronic hepatitis*

|  | <i>Number</i> | <i>Median</i> | <i>Range</i>   |
|--|---------------|---------------|----------------|
| ESR (mm/1 hour Westergren)                           | 38            | 39            | 4 – 125        |
| RCC (10 <sup>6</sup> per microlitre)                 | 22            | 4.2           | 2.7 – 5.0      |
| WCC (per microlitre)                                 | 36            | 5,300         | 2,800 – 11,300 |
| Serum bilirubin (mg/decilitre)                       | 40            | 4.4           | 0.6 – 28       |
| Serum alkaline phosphatase<br>(King Armstrong units) | 40            | 27            | 10 – 150       |
| SGOT (Karmen units)                                  | 39            | 350           | 90 – 3,000     |
| SGPT (Karmen units)                                  | 39            | 320           | 60 – 1,720     |
| Serum pseudocholinesterase<br>(Michel units)         | 34            | 36            | 5 – 119        |
| Prothrombin concentration (%)                        | 24            | 45            | 17.5 – 93      |
| Serum albumin (g/decilitre)                          | 36            | 3.5           | 2.3 – 4.6      |
| Serum $\gamma$ -globulin (g/decilitre)               | 36            | 2.7           | 1.1 – 6.0      |
| Serum IgG (mg/decilitre)                             | 20            | 2,000         | 1,000 – >3,000 |
| Serum IgM (mg/decilitre)                             | 20            | 270           | 86 – >400      |

The ESR varied widely, values of more than 100 mm being recorded in 6 patients and less than 20 in 9 patients. A platelet count of less than 150,000/ml was obtained in almost one-third of patients, the total white cell count was less than 4,000/ml in almost one-quarter of patients and mild anaemia was not uncommon.

Serum bilirubin was less than 1 mg in 3 patients, 1–5 mg in 19 patients, 5–10 mg in 7 patients and more than 10 mg in 11 patients with figures exceeding 20 mg in 4 patients. Serum alkaline phosphatase was usually increased above 15 King Armstrong units and levels of over 30 King Armstrong units were recorded in 13 patients. Serum transaminases were increased to at least twice the upper limit of normal in every case and often reached levels occurring in acute virus hepatitis, being more than 1,000 Karmen units in 12 patients (30 per cent).

Impairment of liver cell synthesizing function was reflected in depressed serum pseudo-cholinesterase, prothrombin and albumin concentrations. Pseudo-cholinesterase was reduced below 53 Michel units in 28 patients (82 per cent) and below 20 Michel units in three patients. Hypoprothrombinaemia was frequent and the prothrombin concentration was less than 30 per cent (Quick one-stage method) in five patients (20 per cent). Serum albumin levels of less than 3 g/dl were recorded in eight patients (22 per cent), but marked hypoalbuminaemia was unusual until the later stages of the disease.

Serum gammaglobulin levels were higher than 1.5 g/dl in 30 patients (83 per cent) and over 3 g/dl in 15 (42 per cent). The serum Ig G and Ig M levels were increased above the upper limit of normal in 60 per cent and 80 per cent of patients respectively.

Serum alpha<sub>1</sub> antitrypsin phenotyping was performed in 20 patients and proved to be Pi M (Pi MM or Pi M-) in all (Glasgow et al 1976). In Northern Ireland this is the commonest alpha<sub>1</sub> antitrypsin phenotype, accounting for more than 80 per cent of individuals in the normal adult population.

In active chronic hepatitis a wide range of antibodies reacting with various tissues may be present in the serum (Doniach et al 1966, Smith et al 1975). Persistently high titres of smooth muscle antibody may be found in two out of three cases and this is an important aid in diagnosis though the antibody is also found in up to half of patients with primary biliary cirrhosis and transiently and in low titre in acute virus hepatitis. Mitochondrial antibody, which has a special relationship to primary biliary cirrhosis where it is found in 90 to 95 per cent of cases, may also be detected in about one-quarter of patients with active chronic hepatitis. Antinuclear factor in a titre of more than 1/20 has been reported in 50 to 60 per cent of cases of active chronic hepatitis, while the incidence of the LE cell phenomenon varies between 15 per cent (Sherlock 1975) and 34 per cent (Soloway et al 1972) and is said to depend upon the diligence of the search and the phase of the disease. The results of the various serological tests are shown in Table IV. The presence of LE cells in 50 per cent of patients, often repeatedly and in large numbers, is noteworthy.

TABLE IV  
*LE cells and serological reactions in patients with  
active chronic hepatitis*

|                                 | <i>Number tested</i> | <i>Number positive</i> |
|---------------------------------|----------------------|------------------------|
| LE cells .....                  | 40                   | 20 (50%)               |
| Antinuclear factor .....        | 39                   | 21 (54%)               |
| Smooth muscle antibody .....    | 38                   | 27 (71%)               |
| Mitochondrial antibody .....    | 37                   | 18 (49%)               |
| Rheumatoid factor - Latex ..... | 17                   | 7 (41%)                |
| - DAT .....                     | 17                   | 2 (12%)                |
| HB <sub>s</sub> Ag .....        | 38                   | 0                      |

#### DIFFERENTIAL DIAGNOSIS

Active chronic hepatitis may be distinguished from a prolonged attack of virus hepatitis and from chronic persistent hepatitis by the presence of various clinical stigmata of chronic liver disease, low serum levels of prothrombin and pseudocholinesterase, hypergammaglobulinaemia, the presence of smooth muscle antibody and the distinctive histological changes in the liver biopsy. Occasionally patients with Gilbert's syndrome are suspected of having active chronic hepatitis because of intermittent or persistent jaundice, fatigue, an indifferent appetite and vague upper abdominal discomfort. However the absence of abnormal physical signs other than mild jaundice, and the completely normal liver tests apart from hyperbilirubinaemia of unconjugated type, obviate the need for liver biopsy.

There are a small number of patients with active chronic hepatitis whose symptoms and signs closely resemble those of primary biliary cirrhosis. They tend to be middle-aged women who complain of troublesome itching and often have persistent mild jaundice. There is disproportionate elevation of serum alkaline phosphatase levels and mitochondrial antibodies are usually present in high titre. This "overlap group" follows a cholestatic course and the response to corticosteroid or corticotrophin therapy is unpredictable and often unsatisfactory. The longterm outlook is appreciably worse in these patients.

Active chronic hepatitis may have to be distinguished from benign recurrent cholestasis, pericholangitis associated with ulcerative colitis, the various hepatic granulomas especially sarcoidosis, alcoholic liver disease, fully developed macronodular cirrhosis, sclerosing cholangitis and primary hepatoma.

#### DISCUSSION

The fundamental cause of active chronic hepatitis is still unknown. It may be due to chronic infection with one of the hepatitis viruses and/or to a disorder of immunity. There is a good deal of indirect evidence in support of both of these

possibilities. It is probable that the disease is not due to a single cause but is a continuing hepatic and systemic response to liver cell injury initially of varied aetiology in genetically predisposed individuals. In the majority of cases, however, it is likely that the initial liver damage is caused by virus infection and in the early stages of the disease the clinical picture may be indistinguishable from acute hepatitis. This was so in 65 per cent of cases in the present series and in some the illness commenced during local epidemics of hepatitis A infection.

This high incidence of illness of acute onset appears to be connected with the unusually frequent occurrence of a positive LE cell test (50 per cent). Rather more than half of these patients had splenomegaly while the median gammaglobulin level (2.9 gms.) was higher than in those with a negative LE cell test. This was also the experience of Soloway et al (1972) who concluded that a positive LE cell test was associated with disease of greater acuteness and severity and with a poorer prognosis in the absence of effective treatment. However they were unable to identify any clinical, biochemical, immunochemical or pathological features that characterised lupoid hepatitis as a separate entity from LE-negative patients. Nevertheless the discovery by Davis and Read (1975) in 42 per cent of their patients with active chronic hepatitis of levels of antibody to double-stranded (native) DNA, usually only found in systemic lupus erythematosus, again raises the question of the relationship between these two conditions. They suggest that these antibodies, previously shown to have a high degree of specificity for systemic lupus erythematosus, may play a specific role in the immunopathogenesis of active chronic hepatitis.

The occurrence in patients with LE-cell-positive active chronic hepatitis of relapses with features indistinguishable from those seen in systemic lupus erythematosus is of considerable interest. Thus during the long hot summer of 1975 a 54-year-old woman taking 7.5 mg of prednisolone daily developed an acute erythematous and oedematous rash across the bridge of the nose, on the cheeks, round the eyes and on the backs of the hands and flitting polyarthralgia with slight swelling and tenderness of some of the limb joints. There was no clinical or biochemical evidence of reactivation of the hepatic lesion and the condition subsided uneventfully with appropriate treatment.

In the knowledge that some cases of non-alcoholic cirrhosis of later life have their beginnings in clinically silent active chronic hepatitis and that with immunosuppressive treatment it is often possible to retard the activity and progress of this disorder, the physician is increasingly conscious of the need to make a firm diagnosis as early as possible. In addition to careful clinical, biochemical and haematological investigation this involves needle liver biopsy. With the widespread use of biochemical screening procedures examples are coming to light of apparently healthy persons with abnormal liver tests of the type seen in active chronic hepatitis (Plotz 1975). Whether or not early treatment of the asymptomatic person with chronic aggressive hepatitis favourably influences possible longterm progression to symptomatic cirrhosis and death has yet to be determined. In the great majority of symptomatic cases of active chronic hepatitis spontaneous remissions tend to be of limited degree and duration. Even in those patients with few

or no remaining symptoms or signs and only minimal changes in liver function tests the histological appearances may still indicate considerably activity of the underlying process. It is therefore probable that other similar cases may pass unrecognised until advanced cirrhosis has developed. By that time the histological appearances of activity may have lessened and if the patient presents with variceal bleeding, ascites or encephalopathy the diagnosis likely to be made is one of cryptogenic cirrhosis.

In this series as in most others, the great majority of patients with active chronic hepatitis were mildly jaundiced at the time of diagnosis. Those who are not may present with unexplained debility, mysterious weight loss, pyrexia of unknown origin, painless hepatosplenomegaly, amenorrhoea, anaemia or polyarthralgia. The diagnosis should always be considered in cases of prolonged hepato-cellular jaundice, especially in women, when a careful history for possible medications is negative and there is a personal or family history of diseases having an immunological basis.

#### SUMMARY

Data from 40 consecutive patients seen at the Royal Victoria Hospital fulfilling the diagnostic criteria of active chronic hepatitis have been analysed in order to gain insight into the many variations that occur in the clinical syndrome. In general the clinical and laboratory findings correspond to those recorded in other series though there were significant differences. The peak age of onset may have been influenced as much by the availability of large specialised hospitals for the care of sick children and for the treatment of infectious diseases as by any real variation in the age incidence. The onset was acute in two-thirds of the patients and insidious in the remaining one-third which is the reverse of experience elsewhere. The LE cell phenomenon was positive in 50 per cent of patients and it is notable that in three-quarters of these the onset of the illness was abrupt and indistinguishable from acute virus hepatitis. There was a close correlation between the incidence of antinuclear factor and a positive LE cell phenomenon while smooth muscle antibodies and mitochondrial antibodies were present in 71 per cent and 49 per cent respectively. Considered in conjunction with the personal and family history of thyroid disease, insulin-dependant diabetes, major allergy and rheumatic fever, and in the light of evidence now becoming available through HL-A histocompatibility studies, there are grounds for believing that genetic influences predetermine susceptibility to active chronic hepatitis. The relationship between this condition and systemic lupus erythematosus requires further investigation.

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